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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,041	02/14/2002	Hideki Ishihara	0397-0440P	6640

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,041	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,11 and 15* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☒ Claim(s) *10* is/are allowed.

6)☒ Claim(s) *1-6,11 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed September 20, 2006 in response to the Office Action of June 20, 2006, is acknowledged and has been entered. Previously pending claims 1, 5, and 10 have been amended. New claim 15 was added. Claims 12-14 were canceled. Claims 1-6, 10, 11, and 15 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Priority

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The certified copy of the Japanese Patent Application No. 2001-37115, the priority document, has been filed.

NEW REJECTIONS

(necessitated by amendment)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Claim 11 recites the limitation "wherein the membrane comprises a hydrophobic part", however, claim 1 no longer recites a membrane. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 15 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein "wherein the thiol is at least one selected from the group consisting of a **mercaptoethanol**..." has no clear support in the specification and the claims as originally filed. THIS IS A NEW MATTER REJECTION.

Applicant points to page 16, lines 2-4, and p. 22, lines 1-19 to support the newly added claim limitation. However, a review of page 16, lines 2-4 and p. 22, lines 1-19 reveals support for using **beta-mercaptoethanol** to stop the reaction. The cited support has been considered but has not been found persuasive because the cited support is not drawn to any mercaptoethanol, it is drawn to one species of mercaptoethanol. The subject matter claimed in claim 15 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 103

NOTE: Applicants amended the claims to remove recitation of "placing the reacted substrate on a membrane", hence the Gray et al (US Patent 6,255,485, issued 7/3/2001, filed 8/6/1998) reference teaching a CDK protein kinase assay using a nitrocellulose membrane no longer applies to the current claims.

6. Claims 1, 2, 3, 6, are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (*J Biol Chem*, 1993, Vol. 268: 20443-20451) in view of Blain et al (Journal of Biological Chemistry, 1997, 272:25863-25872), Jeong and Nikiforv (*BioTechniques*, 1999, Vol. 27: 1232-1238, IDS), and Facemyer and Cremo (*Bioconjug Chem*, 1992, Vol 3: 408-413, IDS).

The claims are drawn to a method for calculating activity of a cyclin-dependent kinase (CDK) in a sample prepared from a living cell, comprising catching the cyclin-dependent kinase by an anti-cyclin-dependent kinase antibody, reacting ATP-γS with a substrate for the CDK in the presence of the CDK in order to introduce a monothiophosphate group into a serine or threonine residue of the substrate, the substrate not containing a sulfur atom, coupling a labeling fluorophore or enzyme with the sulfur atom of the introduced monothiophosphate group of the substrate, measuring an amount of fluorescence from the labeling fluorophore, or reacting the labeling enzyme with a substance to generate an optically detectable product and measuring the amount of the generated product, and calculating the activity of the CDK from the measured amount of fluorescence or the measured amount of the generated product

with reference to a pre-produced curve (claim 1), wherein the CDK is CDK1 (claim 2 and 6), wherein the labeling fluorophore is a fluorescent dye (claim 3), wherein the substrate is a histone H1 substrate (claim 6).

Pan et al. teach a method for calculating or obtaining the activity of cdc2 (CDK1) prepared from a cell sample comprising incubating a CDK1/cyclin complex with [γ-^{32}]ATP and histone H1 and measuring CDK1 phosphorylation activity by quantifying [^{32}P] in the product and comparing it to control measurements (page 20434, col. 1). Pan et al. does not teach reacting ATP-γS with a substrate, catching CDK with an antibody, labeling the substrate with a fluorophore, and calculating the fluorescence from a labeled substrate.

Blain et al teach catching a cyclin-dependent kinase using an anti-cyclin-dependent kinase antibody (immunoprecipitation) for a kinase assay (p. 25864, col. 1).

Jeong and Nikiforv (herein referred to as "Jeong") teach a non-radioactive method of calculating protein kinase activity comprising reacting ATP-γS with a substrate, kemptide (which does not naturally contain a thiol group or sulfur atom), to create a thiophosphorylated product (page 1232, column 3) and measuring fluorescence values in the final product (page 1233, columns 1 and 2). The reference teaches that the biggest drawback of the present method is the relatively slow rate of the biotinylation step, however this can be overcome by various methods and thus it represents a viable alternative to existing methods of screening protein kinases (page 1238, column 2). The reference suggests this method is useful for a wide range of different kinases (page 1232, third column). Further, the reference teaches that

presented is an alternative approach for detecting kinase activity wherein the method does not require the use of radioactivity and allows flexibility in the detection scheme (p.1238, column 2).

Facemyer and Cremo teach a method of using a protein kinase and ATP-γS to create a thiophosphorylated protein and the method of labeling a thiophosphorylated protein by coupling the sulfur of the protein phosphorothioate to a fluorescent haloacetate (page 409). It is noted that the reference further teaches that thiol groups in the substrate are blocked with iodoacetic acid prior to reaction with ATP-γS (See Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate because Blain et al teach the conventionally used method of catching a cyclin-dependent kinase with an antibody for a kinase assay and Jeong specifically teach the disadvantages of traditional assays of enzyme activity of protein kinases which use [γ-^{32}]ATP which require radioactivity and multiple steps. One would have been motivated to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate in order isolate the cyclin-dependent kinase from the cell sample to reduce artifacts from other CDKs and to eliminate the disadvantages specifically taught by Jeong, and because Jeong specifically suggest that the method is useful for a wide range of different kinases.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to substitute the direct fluorescent labeling of the thiol of the

reacted ATP-γS of Facemyer and Cremo for the labeling steps of the combined references because Jeong specifically teach that the biggest drawback of their method is the relatively slow rate of the biotinylation step. One would have been motivated to substitute the direct fluorescent labeling of the thiol of the reacted ATP-γS of the Facemyer and Cremo for the labeling steps of the combined references in order to save not only time, but also the cost of the labeling reagents of Jeong.

7. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al, Blain et al, Jeong and Nikiforv, Facemyer and Cremo, (referred to as "the combined references") in further view of Abo et al (US Patent 5,518,911, issued 5/21/1996).

The claims are drawn to the method of claim 3 wherein the fluorescent dye is FITC (claim 4), the method of claim 1 wherein the labeling enzyme is peroxidase (claim 5). The combined references teach a method for calculating the activity of a CDK as set forth above. However, the combined references do not specifically teach labeling the substrate with FITC or peroxidase.

Abo et al teach a kinase assay of calculating kinase activity of kinase prepared from a cell sample comprising immobilizing (or "catching") the kinase using an antibody (col.27, lines 14-20 and 63-67 to col. 28, lines 1-5; col. 29, lines 60-67 to col. 30, lines 1-5), reacting the kinase with the substrate in the presence of GTPγS (col. 30, lines 16-19; col. 45, Example 14) and labeling the substrate with an enzymatic or fluorescent label

(col. 28, lines 27-67; col. 29, lines 33-36). Abo et al teach that methods of labeling are conventional and known in the art (col. 12, lines 46-47; col. 28, lines 38) and specifically teach the use of FITC and peroxidase as labels (col. 12, lines 50-52).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to label the CDK substrate in the method taught by the combined references with a FITC or peroxidase as taught by Abo et al because Abo et al teach that these methods of labeling are conventional and known in the art. One would have been motivated to label the substrate in the method taught by the combined references using FITC or peroxidase in order to detect the substrate and measure kinase activity. Further, one would have been motivated to substitute the FITC or peroxidase label for the radioactive [^{32}P] label in the method of the combined references because FITC and peroxidase labels offer a safe method for labeling and detecting specific proteins in a sample without the use of hazardous materials such as radioisotopes.

Response to Arguments

8. Applicants argue that Pan et al, Blain et al, Jeong and Nikiforv, Facemyer and Cremo, and Gray et al, each, individually do not teach the step of "calculating the activity of the cyclin-dependent kinase from the measured amount of fluorescence or the measured amount of the generated product with reference to a pre-produced reference curve", therefor, each and every one of the cited references is deficient in disclosing all the claimed features (p. 9-15).

The argument has been considered but is not found persuasive because the rejection in section 4 of the previous Office Action states "Pan et al. teach a method for calculating or obtaining the activity of cdc2 (CDK1) prepared from a cell sample comprising incubating a CDK1/cyclin complex with [γ-^{32}]ATP and histone H1 and measuring CDK1 phosphorylation activity by quantifying [^{32}P] in the product and comparing it to control measurements". Pan et al clearly teaches calculating kinase activity on page 20434, col. 1 and Table III. Histone H1 kinase activity was measured in the absence of cyclin A or B1 to produce a control measurement, wherein the control measurement for kinase activity was 88.2 units, wherein one unit was defined as the incorporation of 1nmol of phosphate into histone H1 after incubation at 30°C for 45 min (see Table III). Pan et al then measures the amount of kinase activity in the presence of substrate H1 and cyclin A or B1 and calculates the activity with reference to the pre-produced measurement as shown in Table III. The incorporation of [^{32}P] was quantitated by liquid scintillation counting (p. 20435, col. 2).

9. Applicants argue that the requisite motivation is lacking, in particular, Pan et al, Blain et al, Jeong et al, fail to disclose catching CDK with an CDK antibody and Facemeyer et al fail to disclose anything regarding CDK as instantly claimed (p. 12).

The argument has been considered but is not found persuasive because Applicants are arguing individual references. The combined references teach the claimed method as set forth above.

10. Applicants argue that the references do not suggest any advantage of catching CDK with an anti-cyclin dependent kinase antibody, reacting ATPγS, etc. as instantly claimed (p. 12).

The argument has been considered but is not found persuasive because the rejection in section 4 of the previous Office Action and in section 6 of the instant Office Action do state advantages for catching CDK with an anti-cyclin dependent kinase antibody and reacting ATPγS. For example: "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate because Blain et al teach the conventionally used method of catching a cyclin-dependent kinase with an antibody for a kinase assay and Jeong specifically teach the disadvantages of traditional assays of enzyme activity of protein kinases which use [γ-^{32}]ATP which require radioactivity and multiple steps. One would have been motivated to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate in order isolate the cyclin-dependent kinase from the cell sample to reduce artifacts from other CDKs and to eliminate the disadvantages specifically taught by Jeong, and because Jeong specifically suggest that the method is useful for a wide range of different kinases."

11. Applicants argue that the deficiencies of Pan et al, Blain et al, Jeong and Nikiforv, Facemyer and Cremo, and Gray et al, as stated in section 8 above are not cured by the addition of Abo et al (p. 13).

The argument has been considered but is not found persuasive because Pan et al, Blain et al, Jeong and Nikiforv, Facemyer and Cremo, and Gray et al teach the claimed invention as set forth above (see section 8), hence there is no deficiency in the references before the addition of Albo et al.

12. All other rejections and objections recited in the Office Action mailed June 20, 2006 are hereby withdrawn.

13. **Conclusion:** Claim 10 appears to be allowable. Claims 1-6, 11, and 15 are rejected. Pan et al, Blain et al, Jeong and Nikiforv, Facemyer and Cremo (see above) teach a method for calculating the activity of a CDK as set forth above. Jeong and Nikiforv teach the step of blocking the kinase reaction with EDTA, a chelating agent (sequestering agent) (p. 1234, col. 1; p. 1236, col. 2), however the references do not teach using a thiol to block the reaction by blocking the labeling agent (claims 10 and 15).

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL

EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER